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WO 96/37177 A1 WO 96/04067 A1 WO 92/19764 A1
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JP 060091262 A

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(54) Abstract Title
Fluid container

(57) A fluid container e.g. in the form of a flexible plastic bag 10 containing blood 20, has an inlet/outlet 11 and usually a sealing valve 12. The container 10 is in communication with a multiple use dignostic test device 51 to 55 for typically detecting bacteria, viruses or opiates in the fluid. A detachable peristaltic pump 40 may be clipped onto tubing joining the container and test device to cause flow of fluid from the container to the device. Testing of the fluid is effected while the container 10 is kept in a sealed condition thus avoiding contamination of the fluid 20 and maintaining it's sterility before it's eventual use.

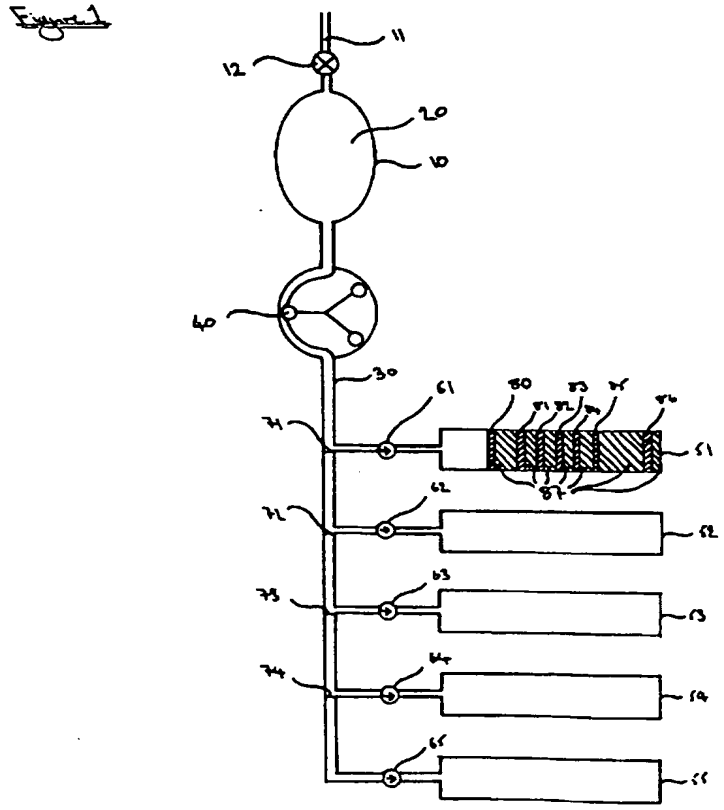

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Figure 1.

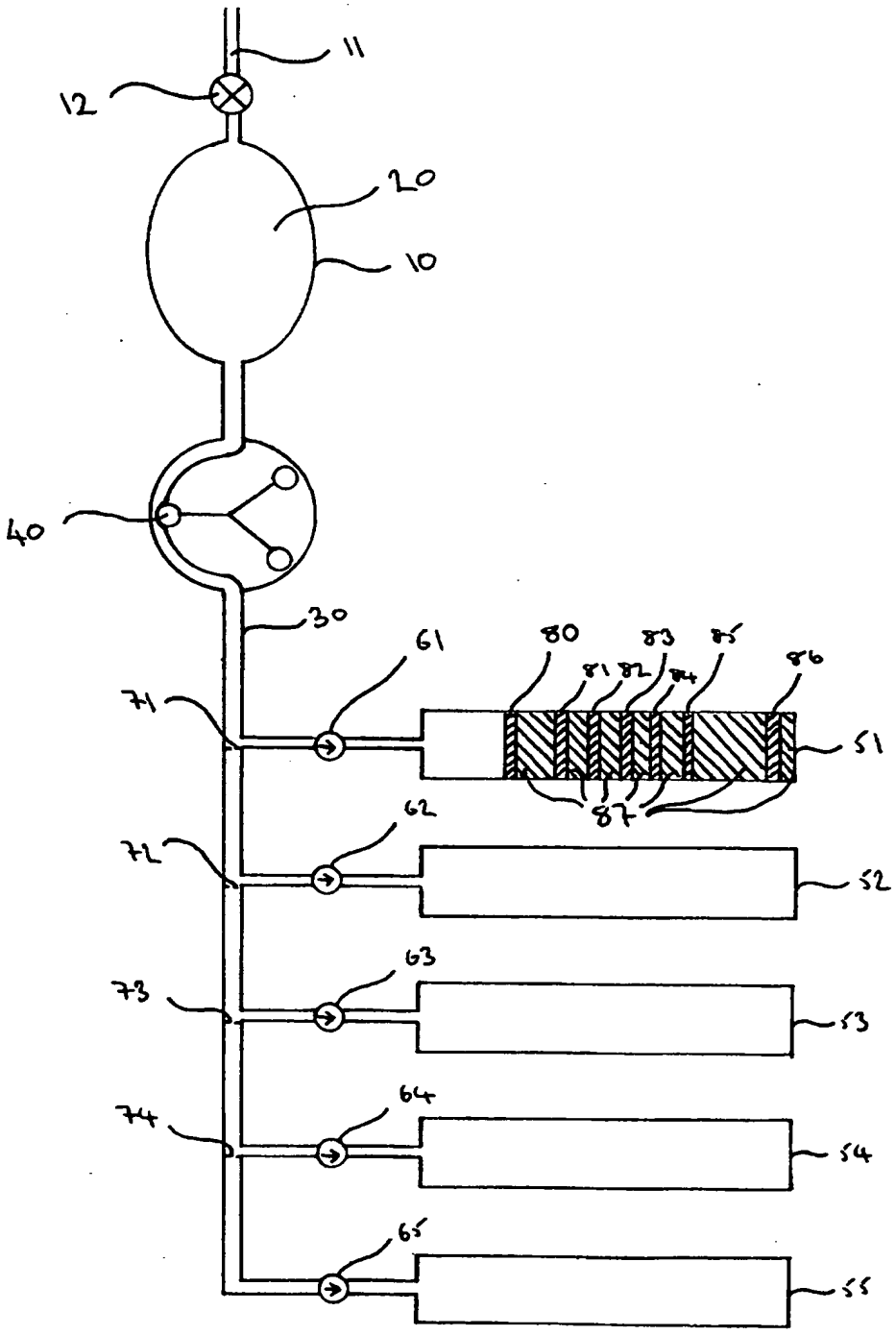
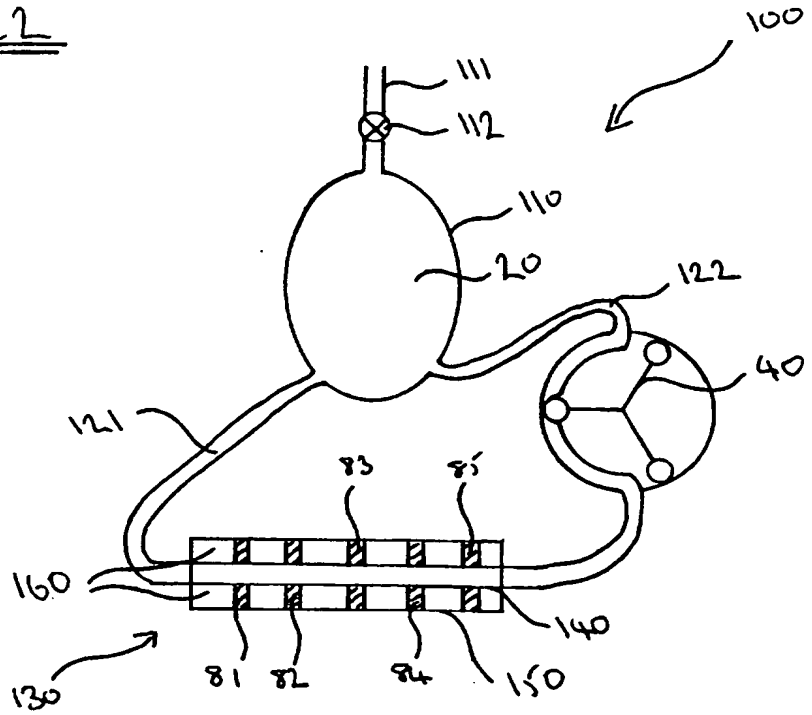


Figure 2



Blood Bag

The present invention concerns sealable fluid containers, particularly containers for biological fluids, and more particularly blood bags, the containers having multiple use diagnostic test means to test their contents whilst the container as a whole is sealed.

Testing of the contents of blood bags has previously been proposed - WO 92/19764 discloses a method and apparatus to detect bacterial contamination of transfusable blood, comprising attaching a flexible blood sample collecting bag to main blood bag by means of a tube through which a sample of blood is passed.

The sample bag contains a bacterial growth medium which allows micro-organisms present in the blood sample to be grown within the sample bag, thereby providing an indication of the presence or absence of contaminating micro-organisms. The test can be carried out immediately prior to transfusion. However, the method of testing requires the growth of bacteria in culture and this takes a numbers of hours, so that an immediate result is not obtainable. Furthermore, the presence of the sample bag containing microbial growth medium in itself poses a risk of contamination in that it provides a bacterial growth medium which may in itself promote the growth of bacteria within the blood, particularly if there is any backflow from the sample bag into the main blood volume.

US 4,945,060 discloses a container having a sealable, sterilizable vessel for detecting the presence of microorganisms in a specimen, the vessel containing a liquid culture medium and a sensor means with an indicator medium therein. Changes in the

indicator medium resulting from pH change or change in carbon dioxide concentration in the medium are detected from outside the vessel.

US 4,182,656 discloses testing for bacterial contamination of a sample by placing the sample in a sealable container containing a culture medium containing a carbon-13 labelled fermentation substrate, the container and its contents being subjected to conditions conducive to biological activity and any $^{13}CO_2$ produced by fermentation detected indicating the presence of biologically active agents (i.e. bacteria) in the sample.

Thus it is known to test the contents of e.g. blood bags to determine their sterility or otherwise. However, they each require e.g. the use of radioactive isotopes or that the seal of the container be broken in order to remove a sample for testing, or provide an environment which potentially encourages a loss of sterility.

Typical hospital practise nowadays means that once a blood sample has been initially collected and cooled, it may be removed from refrigerated storage and allowed to warm on several occasions for possible use in surgical procedures prior to its actually being used. This repeated heating and cooling poses a significant thereat of bacterial growth occurring and means by the time that the blood is finally used it may be contaminated even though it was initially acceptably sterile.

This is also a major problem in the blood re-sale business where blood may be bought from donors of an unknown background and then sold on to other parties who have no guarantee of its sterility or purity (e.g. the absence of narcotics).

The prior art does not provide, nor does it suggest, apparatus or means by which samples may be taken and prepared for use on multiple occasions, the sterilty of the sample being guaranteed before its eventual use.

Thus the prior art does not provide a blood bag (i.e. a fluid container) whose contents can be tested on a number of occasions without potentially effecting contamination. The present invention overcomes the prior art disadvantages.

According to the present invention there is provided a sealable fluid container having multiple use diagnostic test means, comprising a first volume for containing a fluid and communicating with the diagnostic test means, the first volume having an inlet and/or outlet and the first volume being capable of communicating with the test means whilst all inlets and outlets are sealed. The testing means may comprise other than culture medium.

The provision of the testing means for performing a number of tests means that the contents of the container can be tested on a number of occasions for the presence or absence of a particular substance or substances, or of a particular micro-organism such as a bacterium or virus. This is particularly advantageous in the case of blood bags since the sterility of their contents must be assured.

Sealing is achieved by closing all inlets and outlets. The arrangement of the first volume and the test means is such that in order to test a sample of the fluid, the inlet and/or outlet need not to be opened, it therefore not being possible for the testing of a sample to result in contamination of the fluid, i.e. the container remains a sealed unit whilst testing occurs. The container may be any appropriate type of fluid container, but may typically be in the form of a flexible bag such as conventional blood bags.

The container may be used to contain any fluid which may require testing whilst the container is sealed. In particular this includes biological materials such as whole blood, plasma, serum, transfusable blood products such as separated blood factors

(e.g. Factor VIII, immunoglobulins, platelets etc.) or synovial fluids. Other fluids such as urine samples from athletes may be stored and tested in the container.

The first volume may communicate with the test means *via* a one-way valve. Thus during testing reagents may be introduced to the fluid and the reagents prevented from entering the first volume. There may, for example, be a plurality of test means, each having a one-way valve prior to the testing area. As fluid is passed to the testing means for the first time it will enter the first test means and fill it, the fluid being subsequently unable to leave the test means. A single conduit may serve to connect each of the test means to the first volume, supply of fluid along the conduit to each test means being separated by impermeable membranes, each membrane being capable of being ruptured and allowing flow when sufficient pressure is applied, although of course the conduit itself should be capable of withstanding any such pressures.

After the first test means has been used, additional fluid pressure in the conduit may cause the rupturing of a membrane preventing fluid flow to the second testing means. With the membrane ruptured, the second testing means may be used.

A wide range of testing means may be used in the present invention. For example, the testing apparatus of any of WO 96/04068, WO 96/17675, WO 96/17673 or WO/ 96/04067 may be used. Such devices operate by a "flow-through" technique whereby the fluid to be tested is passed over a filter or membrane, the filter or membrane being at a tangent to the direction of flow. The filter or membrane may be provided with desired physical characteristics or other chemical entities (such as enzymes) to filter and/or detect specific molecules in the fluid, the resulting filtrate or reaction products being subsequently detected. This allows a small detection (i.e. testing) area to test a large volume of fluid. To accommodate such large volumes of fluid, the testing means may include a storage volume into which the tested fluid flows. Alternatively it may

additionally communicate with the first volume e.g. have an outlet conduit which returns tested fluid to the first volume. Alternatively, dip-stick type testing means (WO 88/08534) may be used. The provision of a "control" marker (WO 88/08534) may be particularly useful in showing that the test has been successfully completed (irrespective of the result obtained) and for later reference in showing that a particular testing means has previously been used.

The actual reagents used in such testing means will readily apparent to one skilled in the art, for example antibodies (Harlow, E. and Lane, D., "Antibodies - A Laboratory Manual", Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York 1988) specific against a bacterial or viral antigen or an antigen displayed by another pathogen, or against a prion or toxin or narcotic such as an opiate. Other chemical entities which may be used in tests are widely known.

The invention will be further apparent from the following description, with reference to the several figures of the accompanying drawings, which show, by way of example only, forms of blood bag. Of the figures:

Figure 1 shows a sealable blood bag having multiple testing means.

Figure 2 shows a sealable blood bag having a single multiple use test means.

Container 1 comprises flexible plastic container 10 holding blood 20. Plastic container 10 has inlet/outlet 11 and sealing valve 12 to allow the entry and exit of blood 20 as required. Plastic container 10 is attached to tube 30 acting as a conduit between it and testing means 51-55. To cause the flow of blood 20 from plastic container 11 to testing means 51-55, detachable peristaltic pump 40 is clipped onto tube 30 and used. This

causes the flow of blood 20 along tube 30 towards membrane 71 and one-way valve 61. The pressure required for blood 20 to flow through one-way valve 61 is less then that required to rupture membrane 71. Blood flows into test means 51 and encounters filter 80 which prevents the passage of large particles such as platelets. The filtrate then passes along capillary surface 87 upon which is mounted discrete bands of bacterial detecting reagents 81, 82, viral detecting reagents 83, 84, and opiate detecting reagents 85. If the bacteria, viruses or opiates to which the reagents are specific are detected, a colour change in the appropriate band is visible. The filtrate subsequently passes to control band 86, causing a colour change indicating that the test has been successfully completed. Due to the one-way valve 61 controlling the flow of blood, it is not possible for tested blood 20, filtrate or reagents 81-86 to return to plastic container 10. This prevents any contamination of blood 20 in container 10 by reagents 81-86. Control band 86 provides a permanent record showing that testing means 51 has been used.

In a subsequent test of blood 20 in plastic container 10, peristaltic pump 40 is again attached to tube 30 and blood 20 forced through the tube towards membrane 71 and one-way valve 61. This time because of the volume of blood 20 held in testing means 51 the pressure required for blood 20 to pass through one-way valve 61 is greater than that required to rupture membrane 71. As pressure is applied by peristaltic pump 40, membrane 71 ruptures and blood 20 flows towards membrane 72 and one-way valve 62. The pressure required for blood 20 to flow through one-way valve 62 is less than that required to rupture membrane 72. Blood 20 flows through one-way valve 62 into testing means 52 and is tested for bacteria, viruses and opiates.

Container 10 is also provided with temperature sensing strip 90 - rather than allow blood bags to warm to room temperature or body temperature using simple convection heating, other techniques such as microwave heating are nowadays employed. However, this can lead to the excessive heating of fluids if not carefully preformed and

monitored. Temperature sensing strip 90 changes colour if blood 20 is heated to temperature of more than 40°C, at which temperatures protein damage and degradation may occur and pose danger to a patient if infused.

During any testing performed, inlet/outlet valve 12 is not opened and therefore there is no possibility of contamination of blood 20.

In an alternative embodiment, container 100 comprises plastic container 110 having inlet/outlet 111 and valve 112 and containing blood 20. Tubes 121, 122 connect plastic container 110 with testing means 130, detachable peristaltic pump 40 being used to pump blood from plastic container 110 through tube 121 into testing means 130 and back into plastic container 110 *via* tube 122.

Testing means 130 comprises hollow fibre membrane 140 arranged in a "cross-flow" fashion i.e. tangential to the direction of flow of blood 20. Membrane 140 is enclosed by clear plastic outer tube 150 on whose inner surface is deposited discrete bands of reagents 81-85. As blood 20 is pumped through hollow fibre membrane 140 filtrate (not including e.g. platelets) passes through membrane 140 into the volume 160 defined between tube 150 and membrane 140. The filtrate interacts with reagents 81-85 which change colour if the molecule against which they are specific is detected. Blood 20 and filtrate are forced back through membrane 140 by the flow of new filtrate into volume 150, and then flows through tube 122 back into plastic container 110.

The above steps with container 100 can be repeated whenever it is necessary to test blood 20.

It will be appreciated that it is not intended to limit the invention to the above example only, many variations, such as might readily occur to one skilled in the

art, being possible, without departing from the scope thereof as defined by the appended claims.

CLAIMS

1. A sealable fluid container having multiple use diagnostic test means, comprising a first volume for containing a fluid, and communicating with the diagnostic test means, the first volume having an inlet and/or outlet and the first volume being capable of communicating with the test means whilst all inlets and outlets are sealed.

2. A sealable fluid container according to claim 1, being a flexible bag.

3. A sealable fluid container according to either of the preceding claims, the fluid being whole blood, plasma, serum, a transfusable blood product or synovial fluids.

4. A sealable fluid container according to claim 3, the fluid being a transfusable blood product selected from the group of Factor VIII, immunoglobulins and platelets.

5. A sealable fluid container according to any one of the preceding claims, the first volume communicating with the test means *via* a one-way valve.

6. A sealable fluid container according to any one of the preceding claims, the testing means having a fluid inlet and fluid outlet communicating with the first volume, tested fluid being returned to the first volume.

The Patent Office

12

Application No: GB 9815941.1 **Examiner:** Michael R. Wendt
Claims searched: All **Date of search:** 14 October 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): G1B (BBD, BCE, BCF, BCK)

Int Cl (Ed.6): A61J 1/05; C12Q 1/04; G01N 33/50, 33/96

Other: Online: WPI, Claims, Japio

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	WO 96/37177 A1	(NBA) e.g. see Figure 1. Page 13 lines 4 etc. Abstract.	1-4
A	WO 96/04067 A1	(FSM) * referred to in application * e.g. see Figure 7 & page 20 lines 23 etc.	1
A	WO 92/19764 A1	(BAXTER) * referred to in the application * e.g. see Figure 6. Claims 1 & 2.	1 - 4
A	US 4945060	(AKZO) * referred to in the application * e.g. see Figure 1 & Claim 1.	1
X	US 4846005	(BAXTER) e.g. see Figure 2. Column 5 lines 59 etc.	1 - 4
A	WPI Accession No. 85-161616/198527 & JP 060091262 A (DAINIPPON) See Abstract		1

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.